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Award Number: W81XWH-07-1-0283

TITLE: Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure

PRINCIPAL INVESTIGATOR: Paul B. Hicks, M.D., Ph.D.

CONTRACTING ORGANIZATION: TEMPVA Research Group, Inc.
Temple, TX 76504

REPORT DATE: July 2010

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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TEMPVA Research Group, Inc.
1901 S. Veterans Memorial Dr. (151N)
Temple, TX 76504

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: Although selective serotonin reuptake inhibitors (SSRIs) are routinely prescribed for acute stress disorder and early PTSD and recommended in the VA-DoD best practice guidelines, the efficacy of SSRIs as an early intervention for PTSD in service members returning from war-zone duty has still not been determined. Consequently, this study was designed to conduct a controlled trial of fluoxetine as an early intervention for recently redeployed soldiers, as well as to develop methodologies for understanding the multiple factors that may predict outcome. The Brooke Army Medical Center IRB, the regional IRB for the Carl R. Darnall Army Medical Center, has given full approval. A CRADA between TEMPVA Research Group, Inc and the Carl R. Darnall Army Medical Center has been executed. Human Research Protection Office (HRPO) Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) Fort Detrick has been completed and full approval has been given for enrollment. Continuing review was approved in January 2010. Three subjects have been enrolled and recruitment is in progress. A no-cost extension for the next year was requested and approved.

15. SUBJECT TERMS
Fluoxetine, Posttraumatic Stress Disorder, Antidepressants

16. SECURITY CLASSIFICATION OF: U			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
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INTRODUCTION:

Although selective serotonin reuptake inhibitors (SSRIs) are routinely prescribed for acute stress disorder and early PTSD and recommended in the VA-DoD best practice guidelines, the efficacy of SSRIs as an early intervention for PTSD in service members returning from war-zone duty has still not been determined. Consequently, this study was designed to conduct a controlled trial of fluoxetine as an early intervention for recently redeployed soldiers, as well as to develop methodologies for understanding the multiple risk factors that may predict outcome. Fluoxetine was selected as the psychopharmacologic agent for this study because it is well tolerated, it has a very favorable cost-benefit advantage as a generic drug, and the fact that it is the only SSRI with at least preliminary studies demonstrating its efficacy in recent-onset, war-related PTSD. Studies focusing on targeting chronic combat-related PTSD with SSRIs have shown mixed results with some small open-label studies suggesting efficacy, while two controlled trials with Vietnam veterans were negative. In a recent study of survivors of war violence in Europe, Israel, and South Africa, fluoxetine was shown to significantly reduce PTSD symptoms. Because in all prior trials there is considerable variability of response to fluoxetine, we plan to examine several predictors of efficacy. We argue that the efficacy of SSRIs for recently redeployed soldiers at risk for chronic PTSD is moderated by multiple personal, deployment, and environmental factors. It is expected that not all subjects will respond to fluoxetine. For those that do not respond to fluoxetine alone, augmentation with either buspirone or buproprion will be offered based on their reasonable tolerability, low cost and the recent findings documenting their utility as adjunctive treatments for depression.

BODY:

The approval letter has been received from the Brooke Army Medical Center IRB, the regional IRB for the Carl R. Darnall Army Medical Center. The CRADA between TEMPVA Research Group, Inc. and CRDAMC has been executed. The protocol has been approved by the Central Texas Veterans Health Care System IRB and the Research and Development Committee. The Human Research Protection Office (HRPO) of the Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) Fort Detrick has given full approval for initiation of the study. During the last year, space to perform the study became an issue. VA has donated the use of an administrative trailer (12'X52') with sufficient office space to perform the study. The trailer has been completely installed, and is in full use at this time. Twenty-three potential participants have been presented with information regarding the study. Eleven signed a consent form. Seven were excluded because they met one of the exclusion criteria. Three participants were enrolled and are at various stages of the protocol. Recruitment has been much slower than anticipated. We have addressed this by individual meetings with key administrators of clinical programs, grand rounds presentations to Ft. Hood mental health clinicians, and using flyers, approved by the BAMC IRB, which have been placed in strategic places on the Ft. Hood campus. The most successful strategy has been use of the flyers. We continue to investigate ways to make sure that the basic information regarding the project is available to individuals that may be appropriate for participation.

While some turnover of personnel has occurred because of personal reasons, two research assistants are present. One has a master's degree in counseling psychology and the other has a Ph.D. in counseling education. Both have considerable clinical experience, as well as some

research experience. They have been trained on the administration of the psychological tests associated with this project and have developed the casebooks used in data collection, as well as been trained on the use of the CRDAMC electronic medical record system. Credentialing and privileging of Drs. Peggy Pazzaglia and Paul Hicks at the Carl R. Darnall Army Medical Center has been completed and renewed. The Boston VA team under the leadership of Dr. Brett Litz has been assisting in the preparation of the database for recording of the participant data.

The continuing review from the BAMC IRB has been approved (see Appendix). PR064845 is now registered in ClinicalTrials.gov, No. NCT00633685.

Project Tasks:

Task 1: Submission of the Proposal to the IRBs

- The proposal must be approved by both the Brooke Army Medical Center IRB and the Central Texas Veterans Health Care System Human Subjects Subcommittee.
- **Completed**

Task 2: Recruitment and Training of Study Personnel

- Hire two master's prepared research assistants
- Training on recruitment procedures and research assessments (SCID, CAPS, etc.)
- **Completed**

Task 3: Preparation of Over-Encapsulated Blinded Medications for the First Phase of the Clinical Trial

- Purchase of the fluoxetine and gelatin capsules from VA pharmacy suppliers (purchased each 3 months throughout the first 15 months of the study)
- Over-encapsulation of fluoxetine and empty gelatin capsules by CTVHCS Pharmacy staff
- Transfer of medications prepared by the CTVHCS Pharmacy directly to the Carl R. Darnall Medical Center Pharmacy
- The Fluoxetine and placebo capsules have been prepared and transferred to the CRDAMC Pharmacy.
- **Completed**

Task 4: Recruitment/Clinical Trial

- Enrollment of a minimum 20 subjects per month for 15 months
- Double-blind, placebo-controlled trial of fluoxetine + usual psychological care for 12 weeks
- Open-label extension of the fluoxetine trial for 20 weeks
- **In progress**

Task 4: Data Collection and Transfer to the Boston VA National PTSD Research Center

- Data will be stored on compact discs for storage

- Compact discs will be sent on a monthly basis to the National PTSD Research Center for database development
- The post-doctoral fellow working with Dr. Brett Litz will maintain the database under the oversight of Dr. Litz

Task 5: Data Analysis at the Boston VA National PTSD Research Center

KEY RESEARCH ACCOMPLISHMENTS: Recruitment has been initiated.

REPORTABLE OUTCOMES: Not applicable.

CONCLUSIONS: Not applicable.

REFERENCES: Not applicable.

APPENDICES:

Appendix A: BAMC IRB Continuing Review Approval letter, Approved Informed Consent Document, and HIPAA Consent Form
Appendix B: CTVHCS IRB Continuing Review Approval letter
Appendix C: No-Cost Extension of Award Contract
Appendix D: Recruitment Flyer

SUPPORTING DATA: Not applicable

April 2010 IRB

Department of Veterans Affairs

Memorandum

Date: February 5, 2010

From: Paul B. Hicks, M.D., Ph.D.

Subj: Continuing Review of the protocol entitled **"Predictors of Treatment Response to Fluoxetine in PTSD Following A Recent History of War Zone Stress Exposure"** C.2007.145

To: Thomas C. Jefferson, MD
COL, MC
Dept of Clin Invest, BAMC
Dept of Pediatrics and Adol Medicine, BAMC
Consultant for Med Ethics to TSG, US Army
210-916-4495 (DCI)

1. In response to the IRBs 06 January 2010 continuing review of this protocol:

Informed Consent Document:

- The telephone number of the Brooke Army Medical Center Judge Advocate General has been changed to "(210) 808-4075" on page 10. (Attachment A)
- This document had no references to social security numbers.

HIPAA Authorization form:

- This document had no references to social security numbers.

CITI Training:

- Copies of current CITI certificates for LTC Michael Adams and Keith Young, Ph.D. are in Attachment B.

Concur
mwd 26 FEB 10

2. An expedited review is requested for the following changes:

HIPAA Authorization form:

- Add Research Assistant, Kamau Richard, MS, LPC-Intern as having access to participant information. He is fully trained with all paperwork on file in the Research Office including a Scope of Practice, Conflict of Interest, and Certificates of Training. He has received training and is competent to function in his assigned position. (Page 2; Attachment C)
- Note: "effective until 01 March 2010" added to Research Assistant Natalie Reeves (page 2; Attachment C)
- Add Brett Litz, PhD, Associate Investigator, as having access to participant information as he may be reviewing audio recordings of assessments. He is fully

Expedite Review Approved. 45 CFR 46.110 and 21 CFR 56.110 and 21 CFR 312.120
Jorge C. Cabrera MD
17 March 2010
IRB, Member

MAR 17 2010

trained and credentialed with all paperwork on file in the Research Office including a Scope of Practice, Conflict of Interest, and Certificates of Training. He is qualified to perform the duties required of the position. (Page 2; Attachment C)
- Clarity to the mailing address for Michael L Adams, PhD, LTC (ret) has been made to assure any letters sent to him would be expediciously received. (pages 2 and 3; Attachment C)

CITI Training:
- New CITI certificate for Kamau Richard included in Attachment B.
- CITI certificate for Brett Litz as well as recently updated certificates for Paul Hicks and Leah Blackburn included in Attachment B.

Protocol:
- Updated to reflect new Research Assistant, Kamau Richard and last date of Natalie Reeves (page 2; Attachment D)
- Updated to reflect Brett Litz may see participant PHI in the form of audio recordings (page 2; Attachment D)

Paul B. Hicks, MD, PhD

Paul B. Hicks, M.D., Ph.D.
Overall Principal Investigator

Attachments

CC: Michael L. Adams, Ph.D., LTC (Ret)

BROOKE ARMY MEDICAL CENTER/CARL R. DARNALL ARMY MEDICAL CENTER
INFORMED CONSENT DOCUMENT
Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure

Site Principal Investigator: Michael L. Adams, Ph.D., LTC (Ret.)
Principal Investigator: Paul B. Hicks, M.D., Ph.D. (Central Texas Veterans Health Care System; Temple, Texas)

Research Study Funded by Department of Defense

We are asking you to volunteer to take part in a research study at the Carl R. Darnall Army Medical Center. It is important that you read and understand the information on this form. If you choose not to participate in this research study, your decision will not affect your eligibility for care or any other benefits to which you are entitled.

DESCRIPTION/PURPOSE OF RESEARCH:

You are being asked to consider participation in this research study. The purpose of this study is to determine whether the medication fluoxetine, often used to treat depression, is an effective treatment for posttraumatic stress disorder (PTSD) and associated conditions in soldiers with recent war-zone exposure, as well as determine whether any response to fluoxetine is related to the degree of trauma exposure, the severity of PTSD symptoms, resistance to psychological trauma, adequacy of social supports (family, extra-military and military), the degree of post-deployment stressors and life problems, or the degree of any loss of memory. Many soldiers exposed to war-zone stress do not appear to have subsequent problems, however, as many as 20% (or one in five) will develop significant mental health problems because of their war exposure. The fact that such a significant number of soldiers have difficulty adapting to life after war exposure suggests that we need to have well-defined, affordable treatments that are effective. Currently, recommendations for medications to manage PTSD focus on the use of commonly prescribed antidepressants such as fluoxetine. Despite this recommendation by the Department of Defense (DoD)/Veterans Administration (VA) Clinical Practice Guidelines, there have not been any studies evaluating the effectiveness of these medications in patients that have recently been exposed to war-zone stressors. In fact, studies in Vietnam-Era veterans have shown limited effectiveness of these medications for PTSD. Also, there is very limited information available to understand the factors that influence whether a particular soldier will respond to treatment with these antidepressants. The procedures of this study will help identify which individuals with PTSD are likely to benefit from these medications.

This study will enroll approximately 300 subjects at the Carl R. Darnall Army Medical Center, over a period of three years. During your participation in this study, you will be asked to make approximately 11 one to two hour outpatient visits with Dr. Paul Hicks or other supporting staff at the Resilience and Restoration Center of the Carl R. Darnall Army Medical Center. This study involves the investigational (research) use of a drug called fluoxetine (the generic equivalent of Prozac). The Food & Drug Administration (FDA) has not yet approved this drug for treating PTSD.

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However, the FDA has not objected to its use to study its safety and effectiveness. The safety of fluoxetine (Prozac) in humans has been tested in prior research studies. Fluoxetine has been prescribed to millions of patients experiencing depression.

INCLUSION AND EXCLUSION CRITERIA:

To qualify for this study you must:

1. Be a veteran of the Operation Enduring Freedom/Operation Iraqi Freedom war campaigns with trauma exposure sufficient to qualify for a diagnosis of PTSD.
2. Meet criteria for a diagnosis of PTSD as determined by a standard questionnaire of symptoms, and have a minimum score on that questionnaire.
3. If you are female, you must have a negative serum pregnancy test and agree not to become pregnant for the duration of the study.

You will not be allowed to participate in this study if:

1. It is known that you are not able to tolerate fluoxetine.
2. It is known that you do not respond to fluoxetine at 60 mg daily.
3. You have a history of a significant mental disorder other than PTSD.
4. You have a significant history of suicidal or homicidal behavior/thoughts.
5. You have a history of dependence on any substances in the past 6 months.
6. You have a serious general medical condition that would prevent you from completing the study.
7. You have been using medications for depression or other mental health conditions except for zolpidem (Ambien) for the two weeks prior to beginning the study.
8. You are female and are found to be pregnant.
9. You have participated in another research drug trial within 30 days of enrollment.

PROCEDURES:

If you volunteer to participate in this study, we will ask you to do the following things:

1. If you are a qualified candidate and you agree to take part, the doctor or research staff will obtain your written informed consent to participate in this study. If you do participate, you must agree to carefully follow all the instructions that you are given.
2. Your medical history will be obtained and you will be physically examined by a physician associated with the study. For your own safety, it is your responsibility to tell the doctor all of your past and present diseases, allergies and medical conditions that you are aware of and all drugs and medications that you currently take.
3. Your height, weight, and blood pressure will be recorded.
4. A tablespoon (15 ml) of blood will be obtained at the first visit and at the sixth visit to estimate the degree of effect fluoxetine is producing on your brain chemistry.

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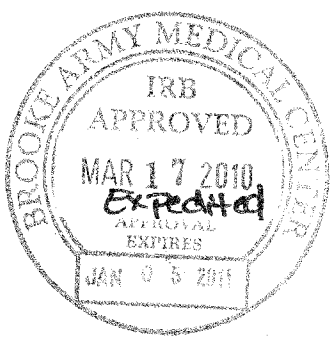
5. Since this research may have bad effects on an unborn child and should not be performed during pregnancy, it is necessary that a pregnancy test be done first. If you are female a serum pregnancy test will be performed. To your knowledge, you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.
6. As a participant, you will be asked to participate in two phases of this study. In the first phase, you will be randomly assigned to one of two treatments. Randomization is a process like flipping a coin and means you will have an equal chance of being assigned to either of the treatments. One of the two treatments will require you to take the study medication, fluoxetine (150 subjects), in increasing doses from 20 to 60 mg daily for a 12-week period. A second group will be assigned to receive placebo (150 subjects). A placebo is an inactive, harmless substance, like a sugar pill, that looks like the other study medications. You will have a one in two chance of being in the placebo group. The first phase of this study is a double-blind study, which means that neither you nor your providers will know whether you are receiving the study medication or a placebo. In the event of an emergency, however, there is a way to determine which you are receiving. **All subjects will continue to receive psychological treatments from their providers in the Resilience and Restoration Center at the Carl R. Darnall Army Medical Center throughout the study.**
7. In the second phase of this study you will be given fluoxetine in increasing doses, as needed, up to 80 mg daily for an additional 20 weeks. If you do not have significant improvement (greater than 50%) after being given 80 mg daily of fluoxetine for 4 weeks, then you will be assigned to also receive either bupropion SR (generic equivalent of Wellbutrin at 150 mg daily) or buspirone (generic equivalent of Buspar at up to 40 mg daily) for the remainder of the 20-week period in an attempt to improve your response to fluoxetine.
8. If you have trouble sleeping, you may be given a prescription for zolpidem (generic equivalent of Ambien).
9. The total participation time, including both phases of the study, will be 8 months duration.
10. The use of other prescription or over-the-counter medicines will not be allowed without your study doctor's approval. You will need to take part in regular outpatient visits while taking the study medication and must tell the doctor of any effects that you experience. During the study you should continue your normal dietary habits and vitamin intake. The use of tobacco will also be allowed during the study.



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11. You will be asked to complete questionnaires and answer questions about your symptoms and feelings at the beginning of the study and also at weeks 2, 4, 6, 8, 12, 16, 20, 24, 28 and 32. The tests will normally be completed in about 30-45 minutes. The testing will take longer (up to 2 1/2 hours long) before the start of the 1st, after the 12th week of treatment, and after the 32nd week. Approximately 25% (one-fourth) of the interviews will have audio recordings made so that reliability of the questionnaire measurements can be assessed. After reliability measurements are completed, the audiotapes will be destroyed. The questionnaires will require you to answer questions about:
    - Your demographic information (e.g., age, race, education, etc.) and military service (e.g., rank, the number of years in the Service, etc.)
    - Any trauma you have experienced during your life
    - The amount of your combat exposure
    - Your symptoms and feelings, including anxiety, depression and PTSD symptoms
    - The stress and adversity your family has experienced since your deployment
    - The quality of your family relationships and social supports
    - The quality of your peer and leader supports
    - The quality of your physical health, activities of daily living, and overall life satisfaction
    - Your ability to withstand stressful events
    - Your memory, attention, and ability to use language
    - Whether there are any bad side effects to your study medications
    - Which medications you are taking
    - Your current use of alcoholic beverages
    - Your guess as to which treatment you are receiving
    - Your treatment expectations
12. Study personnel will also regularly assess your response to treatment and will ask detailed questions about the treatment effects and side effects. If your condition gets worse, the study medication may be stopped and you will be given other medication instead. If your condition improves you must still return for further visits until the study has finished.
13. If you need a procedure requiring additional informed consent, a separate consent form will be given to you before that procedure.
14. We will obtain information from your medical records concerning laboratory test results, medical diagnoses, pharmacy records, clinic and hospital visits, and any procedures performed.
15. Your name will not be mentioned in research publications that result from this study.
16. We cannot guarantee that you will be able to continue receiving fluoxetine after this study is over, but fluoxetine may be available through your family doctor.

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RISKS, STRESS OR DISCOMFORT:

The potential side effects associated with the administration of fluoxetine include:

- nausea
- diarrhea
- restlessness
- headache
- sleeplessness
- inability to perform sexually (e.g. impotence, inability to have an orgasm, decreased sex drive)
- drowsiness
- tremors (shaking).
- If you receive placebo there may be less benefit and therefore the symptoms of PTSD may be present for a longer time
- In May 2007 the FDA approved the following additional information about the use of all antidepressants. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Antidepressant medicines may increase suicidal thoughts or actions in some teenagers and young adults when the medicine is first started. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. You may wish to advise your family and/or caregiver of your involvement in this study.**

Zolpidem may cause:

- drowsiness, the intended benefit
- diarrhea
- nausea
- dry mouth
- muscle aches
- dizziness
- headaches
- confusion
- depression

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Buspirone may cause:

- nausea
- dizziness
- headache
- blurred vision
- agitation

Bupropion SR may cause:

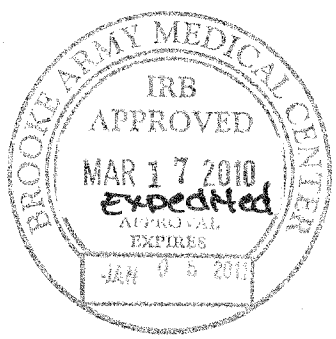
- elevated blood pressure (hypertension)
- increased heart rate (tachycardia)
- rash
- sweating
- constipation
- nausea
- dry mouth
- confusion
- dizziness
- insomnia
- hostility
- tremor
- seizures (convulsions)

Other side effects may occur, some of which are not known and cannot be predicted. If you follow instructions and help the staff perform the appropriate examinations and laboratory tests, the chance of these unwanted side effects happening can be kept to a minimum. If side effects occur, you should contact the staff so that appropriate step to reduce them can be taken.

Some clients may experience some disruption of daily activities due to scheduling of the evaluation sessions. Also, answering questions that evoke painful memories will likely be uncomfortable for many subjects. Although you are free to decline to answer any questions you find objectionable, it is important for the purpose of this study that you try to answer all questions.

Pain, bruising, *and* rarely, fainting or infection may occur when blood is drawn on the first and sixth visits.

Consented participants, under the supervision of the study's psychiatrist(s), must discontinue any current psychotropic medication(s) prior to randomization in the study and may experience: worsened memory, increased depression, anxiety, or suicidal thoughts. Other side effects may occur



during this period, some of which are not known and cannot be predicted. Side effects encountered will vary depending on the medication, dosage, diagnosis the medication is prescribed for, length of time it has been taken, characteristics (physical and mental) of the individual, etc. You are expected to keep the research staff informed of any and all effects/experiences you encounter during the medication discontinuation phase.

It is possible that the study medication may not be effective and that your condition may worsen. If, in the opinion of your study doctor, there are any problems caused by the study medication that make it unwise for you to continue taking it, you will be withdrawn from the study and appropriately treated by your doctor.

If you are a FEMALE OF CHILD BEARING POTENTIAL wishing to volunteer for this project, you must understand that fluoxetine, buproprion SR, zolpidem or buspirone might be harmful to (1) an unborn child if you are pregnant; or (2) an infant if you are breast-feeding. Studies evaluating the capability of the medication under investigation to produce birth defects in an unborn child have not been conducted. Therefore, you must not be pregnant during the study and will be required to take a pregnancy test before you participate in this study. You must also agree to take precautions to prevent pregnancy during the course of this study due to the possible severe harm the drug/procedure may cause your unborn child. The only completely reliable methods of birth control are total abstinence or surgical removal of the uterus. Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products may not be totally effective in preventing pregnancy. Also, you must not breast-feed and participate in this study.

If you become pregnant or feel you might be pregnant, contact your provider and the study investigator listed in the Voluntary Participation section.

You will be kept informed of any significant new findings occurring during the course of the research that may influence your willingness to continue to participate in the study.
If you have any questions regarding the research, your participation, or suspect any research-related illness or injury, contact: **Dr. Michael Adams** at (254) 553-0921 or **Dr. Paul B. Hicks** at (254) 743-2643. After hours you may contact Dr. Paul B. Hicks, at (254) 760-8309.

BENEFITS:
The investigators have designed this study to learn if the new treatment is as good as or better than or worse than the most commonly accepted treatments. However, there is no guarantee or promise that you will receive any benefit from this study. The possible benefit of your participation in this study is that subjects are likely to receive some symptomatic improvement with the combination of psychological and pharmacological interventions offered in this study. If response is experienced,

the subject will have symptomatic improvement and will likely be able to better adapt to current stressors in their life.

There is no guarantee you will receive any benefit from this study other than knowing that the information may help future patients.

PAYMENT (COMPENSATION):
You will be paid $50 for each blood draw for a maximum of $100 for two blood draws.

ALTERNATIVES TO PARTICIPATION:
Participation in this study is entirely voluntary. **You may refuse to participate or may withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled.** If you decide to withdraw from the research study, notify the staff and/or study doctor of your intention to do so. The study doctor may stop your participation if it is determined to be in your best interest or if you fail to follow the directions of the study doctor.

You do not have to participate in this study to receive treatment for your condition. The medication involved in this study may also be available through your family doctor without the need for you to volunteer to participate in this study. Other drugs are available as alternatives to the drugs being tested in this study. These alternative medications include sertraline (Zoloft®), citalopram (Celexa® or Lexapro®), which are approved for the treatment of PTSD.

RESEARCH RESULTS
1. During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.
2. All questionnaires and study materials will remain in the possession of the investigators at the Carl R. Darnall Army Medical Center. Only the investigators and their research associates will have access to these materials. They will be stored in a secured, locked location for three years after the completion of the study. All questionnaires and all study materials will remain in the possession of the investigators at the Carl R. Darnall Army Medical Center in building 36009 for a minimum of five years after the completion of the study. They will be stored in a secured and locked cabinet, accessible only by the Overall Principal Investigator, Site Principal Investigator, Research Psychiatrist, and two Research Associates, all of whom will have a key. All study materials, questionnaires, notes, samples, and audiotapes, will be coded prior to usage and the key to the code will be kept by the pharmacy and research personnel in a locked drawer.

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Data will be securely stored in a de-identified manner. Biological samples will be coded at the time the sample is drawn and the de-identified samples will be transported to the CTVHCS lab for analysis and disposal. De-identified electronic media will be shipped via an established nationwide delivery company (e.g.: FedEx) to the Co-Principal Investigator at the National Center for PTSD, VA Boston Health Care System. Five years after closure of the study, any and all paper AND electronic documentation containing confidential, personally identifiable information, protected health information, and any other sensitive information will be disposed/destroyed according to current VA regulations at the time of disposal/destruction of documentation.

3. If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. Your medical records will be maintained according to Department of Defense (DoD) requirements.

CONFIDENTIALITY OF RECORDS OF STUDY PARTICIPATION:

Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. Your records may be reviewed by the U.S. Food & Drug Administration (FDA), other U.S. government agencies, the Brooke Army Medical Center Institutional Review Board, representatives of the US Army Medical Research and Materiel Command (USAMRMC), the Central Texas Veterans Health Care System (CTVHCS) Institutional Review Board. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others. Complete confidentiality cannot be promised, particularly for military personnel, because information regarding your health may be required to be reported to appropriate medical or command authorities.

Confidentiality may be broken should you tell us you have thoughts of suicide, hurt/kill someone else, or any instances of current abuse of children, elders, or persons with disabilities.

By signing this consent document, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for educational purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data.

ENTITLEMENT TO CARE:

In the event of injury resulting from this study, the extent of medical care provided is limited and will be within the scope authorized for Department of Defense (DoD) health care beneficiaries.

BROOKE ARMY MEDICAL CENTER/CARL R. DARNALL ARMY MEDICAL CENTER
INFORMED CONSENT DOCUMENT
Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure

Your entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations, and if you have questions about your rights as a research subject or if you believe you have received a research-related injury, you may contact the Brooke Army Medical Center Protocol Coordinator at (210) 916-2598 or the Brooke Army Medical Center Judge Advocate General at (210) 808-4075 or the Carl R. Darnall Army Medical Center, Judge Advocate General, (254) 286-7339.

SPECIAL INFORMATION:

1. You are not required to take part in this study: your participation is entirely voluntary.
2. You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment, if you are a patient.
3. There will be no costs to you for any of the treatment or testing done as part of this research study.
4. If you have questions about your rights as a research participant, you may contact **Dr. Michael Adams** at (254) 553-0921.
5. If you are a patient, this consent form will be placed in your medical record and a copy will be kept in the research office.

VOLUNTARY PARTICIPATION:

The decision to participate in this study is completely voluntary on your part. No one has coerced or intimidated you into participating in this project. You are participating because you want to. The Principal Investigator or one of his associates has adequately answered any and all questions you have about this study, your participation, and the procedures involved. If significant new findings develop during the course of this study that may relate to your decision to continue participation you will be informed.

You may withdraw this consent at any time and discontinue further participation in this study without affecting your eligibility for care or any other benefits to which you are entitled. Should you choose to withdraw, you must contact Dr. Paul Hicks or a member of the study staff at the following number (254) 743-2643 or **Dr. Michael Adams** at (254)553-0921. You will be asked to complete end of study procedures. There are no consequences if you do not complete these procedures. Your condition will continue to be treated in accordance with acceptable standards of medical treatment. If you withdraw your consent, researchers may only use and disclose the information already collected for this study and, your information may still be used and disclosed should you have a bad effect.

The investigator of this study may terminate your participation in this study at any time if he/she feels this to be in your best interest. If you become ill during the research, you may have to drop out,

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even if you would like to continue. The investigator will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

CONTACT INFORMATION:

Site Principal Investigator (PI)

The Site Principal Investigator or a member of the research staff will be available to answer any questions concerning procedures throughout this study.
Site Principal Investigator: **Dr. Michael Adams** at (254) 553-0921

In addition, the Principal Investigator will also be available to answer questions concerning procedures throughout this study.
Principal Investigator: **Dr. Paul B. Hicks** at (254) 743-2643

You have read the information provided above. You have been given an opportunity to ask questions and all of your questions have been answered to your satisfaction. You have been given a copy of this form. You agree to participate in this study on a voluntary basis. All oral and written information and discussions about this study have been in English, a language in which you are fluent.

A copy of this signed and dated form will be given to you.

_____	_____	_____
Volunteer's Signature	**Phone #**	**Date**
_____	_____	
Volunteer's Printed Name	**Date of Birth**	

_____
Volunteer's Address (street, city, state & zip code)

_____	_____	_____
Advising Investigator's Signature	**Date**	**Phone Number**

(can only be signed by an investigator whose name is listed in the protocol)

BROOKE ARMY MEDICAL CENTER/CARL R. DARNALL ARMY MEDICAL CENTER
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH
(APHI Template Version 3, February 04)

You are being asked for permission to use or disclose your protected health information for research purposes in the research study entitled "*Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure*".

The Health Insurance Portability & Accountability Act of 1996, Public Law 104-109 (also known as HIPAA), establishes privacy standards to protect your health information. This law requires the researchers to obtain your authorization (by signing this form) before they use or disclose your protected health information for research purposes in the study listed above.

Your protected health information that may be used and disclosed in this study includes:

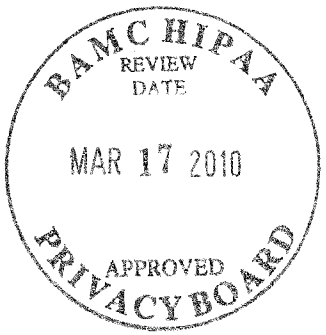
- Demographic information (e.g., age, race, education, etc.) and military service (e.g., rank, the number of years in the Service, etc.)
- Medical History/Surgical History
- Laboratory Results
- Responses to questionnaires
- Frequency, duration, content, and type of therapy treatment sessions with your current Usual Care Clinician (therapist)

Your protected health information will be used for:

The purpose of this study is to determine whether the medication fluoxetine, often used to treat depression, is an effective treatment for posttraumatic stress disorder (PTSD) and associated conditions in soldiers with recent war-zone exposure, as well as determine whether any response to fluoxetine is related to the degree of trauma exposure, the severity of PTSD symptoms, resistance to psychological trauma, adequacy of social supports (family, extra-military and military), the degree of post-deployment stressors and life problems, or the degree of any loss of memory.

The disclosure of your protected health information is necessary in order to be able to conduct the research project described. Records of your participation in this study may only be disclosed in accordance with state and federal law, including the Privacy Act (5 U.S.C. 552a) and the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations (45 CFR 160 & 164). Note: Protected health information of military service members may be used or disclosed for activities deemed necessary by appropriate military command authorities to ensure the proper execution of the military mission.

By signing this authorization, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for educational purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data.



The Principal Investigator may use and share your health information with:

- The Central Texas Veterans Health Care System Institutional Review Board and the Brooke Army Medical Center/Carl R. Darnall Army Medical Center Institutional Review Board
- State and Federal Government representatives, when required by law
- Brooke Army Medical Center/Carl R. Darnall Army Medical Center Department of Defense representatives
- Representatives of the US Army Medical Research and Materiel Command (USAMRMC)
- Other collaborating investigators:
    - Paul B. Hicks, M.D., Ph.D.
      Central Texas Veterans Health Care System
    - Brett Litz, Ph.D.
      VA Boston Health Care System
    - Peggy Pazzaglia, M.D.
      Central Texas Veterans Health Care System, Psychiatrist
    - Leah M. Blackburn, M.A., L.P.C.
      Central Texas Veterans Research Foundation, Research Assistant
    - Kamau Richard, M.S., L.P.C.-Intern
      Central Texas Veterans Research Foundation, Research Assistant
    - Natalie Reeves, M.S., L.P.C. (effective until 01 March 2010)
      Central Texas Veterans Research Foundation, Research Assistant

The researchers and those listed above agree to protect your health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and federal law.

You need to be aware that some parties receiving your protected health information may not have the same obligations to protect your protected health information and may re-disclose your protected health information to parties not named here. If your protected health information is re-disclosed, it may no longer be protected by state or federal privacy laws.

You do not have to sign this Authorization. If you decide not to sign the Authorization:

- It will not affect your treatment, payment or enrollment in any health plans or affect your eligibility for benefits.

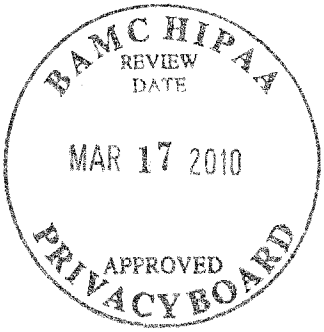
- You may not be allowed to participate in the research study.

After signing the Authorization, you can change your mind and:

- Notify the researcher that you have withdrawn your permission to disclose or use your protected health information (revoke the Authorization).

If you revoke the Authorization, you will send a written letter to:

Michael L. Adams, Ph.D., LTC Ret.



R&R Center: Urgent Care & Triage Clinic
36000 Darnall Loop
Ft. Hood, TX 76544-4752

to inform him of your decision.

- If you revoke this Authorization, researchers may only use and disclose the protected health information already collected for this research study.
- If you revoke this Authorization your protected health information may still be used and disclosed should you have an adverse event (a bad effect).
- If you withdraw the Authorization, you may not be allowed to continue to participate in the study.

During your participation in this study, you will not be able to access your research records. This is done to ensure the study results are reliable. After the completion of the study, you have the right to see or copy your research records related to the study listed above. A Request for Access must be made in writing to:

Michael L. Adams, Ph.D., LTC, Ret.
R&R Center: Urgent Care & Triage Clinic
36000 Darnall Loop
Ft. Hood, TX 76544-4752

If you have not already received a copy of the brochure entitled "Military Health System Notice of Privacy Practices," you may request one. DD Form 2005, Privacy Act Statement - Military Health Records (located on your medical records jacket), contains the Privacy Act Statement for the records. If you have any questions or concerns about your privacy rights, you should contact the Brooke Army Medical Center Privacy Officer at phone number (210) 916-1029 or Central Texas Veterans Health Care System Privacy Officer at 1-800-423-2111, ext 42055.

This Authorization does not have an expiration date.

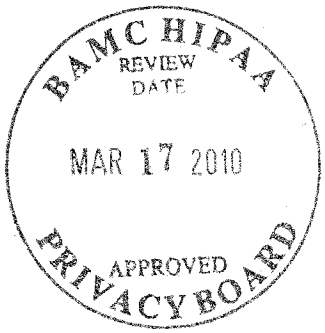
You are the subject. You have read this information, and will receive a copy of this form after it is signed.

I consent to the release of the above stated information from _____, my off-post Usual Care Clinician (therapist).
(print therapist name)

_____ _____
Volunteer's Signature **Date**

_____
Volunteer's Printed Name

_____ _____
Signature of Witness **Date**



IRB APPROVAL - Amendment

Date: October 16, 2009
From: Marjory Williams, Ph.D., R.N., Chairperson
Investigator: Paul B. Hicks, M.D., Ph.D.
Protocol: Predictors of Treatment Response to Fluoxetine in PTSD Following A Recent History of War Zone Stress Exposure
ID: 00308 Prom#: 0016 Protocol#: N/A

The following items were reviewed and approved at the 10/14/2009 meeting:

- Consent Form - BAMC Approved ICD (08/05/2009)
- Memo from PI with study changes and approvals (09/28/2009)
- E-mail from CIV USA MEDCOM USAMRMC (09/10/2009)
- Memo from BAMC IRB (08/05/2009)
- BAMC Protocol for Clinical Invest-Human (06/01/2009; 3)

1. The IRB members reviewed and approved the above protocol amendment, which consisted of approval letters from VAMC IRB (IRB of record) and USAMRMC HRPO ORP; approved (stamped) Informed Consent Document and HIPAA Authorization; and current Protocol. The IRB members accepted the above amendment in accordance with the Office for Human Research Protections (OHRP) memorandum dated October 16, 2008, regarding Guidance on Engagement of Institutions in Human Subjects Research, Part IV, IRB Review Considerations for Cooperative Research.

2. The above amendment was approved using OHRP guidance as it is approved for the IRB of record will be the Brooke Army Medical Center (BAMC), which operates under FWA00004092. The amendment is approved as submitted.

3. As stated above, this study is approved with BAMC as the IRB of record. The CTVHCS IRB oversees the study to ensure it is operating in accordance with VA and Federal policies and procedure, but is not the IRB of record.

4. You are complying with the institutional requirements for human subject protection. If the protocol or waiver of informed consent form is modified in any way or discontinued for any reason before the next continuing review, please notify the Subcommittee.

5. Thank you for your cooperation and for your support of our efforts to protect human subjects and their protect health information.

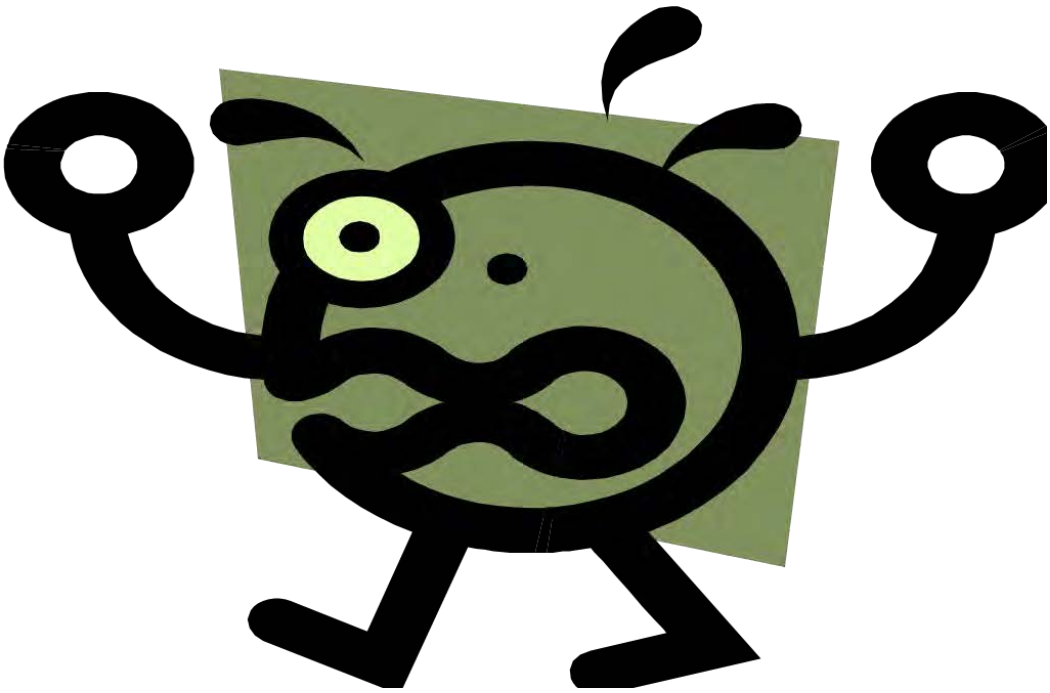
6. If additional information is needed please contact Lorrie Thomas, Program Specialist, at extension 41974.

Marjory D. Williams, Ph.D., R.N.
CTVHCS, IRB Chairperson

APPROVED
BAMC IRB

Jun 30 2010

IRRITABLE?
TROUBLE SLEEPING?
FLASHBACKS?
BAD DREAMS?
FEELING EMOTIONALLY NUMB?



The VA and the DOD are performing a clinical drug trial
to improve treatment of PTSD.
If you were involved in a traumatic event during OEF/OIF,
feel you may suffer from PTSD,
and would consider participation in this study
call **(254) 534-0370** or **(254) 534-1044** for more information.

LOCATION: between Resilience & Restoration Center (36003) and Urgent Care & Triage Clinic (36009)